Indian Journal of Gastroenterology (May–June 2018) 37(3):183–185
https://doi.org/10.1007/s12664-018-0852-y

EDITORIAL

Is the emergence of inflammatory bowel disease a prime example of "the third epidemiological transition"?

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Received: 17 April 2018 / Accepted: 8 May 2018 / Published online: 12 June 2018

Inflammatory bowel disease (IBD) burden is increasing at a rapid pace in India and other Asian countries and with total population into consideration, India is projected to have among the highest IBD burden across the globe, despite having lower prevalence as compared to the West [1, 2]. Although the IBD genetic architecture of India and West exhibits both similarities and differences, the overall genetic risk of Indians is like that in the West as demonstrated by the similar susceptibility to disease in second-generation Indian immigrants living in high prevalence areas [2]. The microbiota signature of Indian IBD patients is also similar as shown by matching perturbations in the structural and functional component of gut microbiota in Indian studies [3, 4]. While the incidence and prevalence of IBD have stabilized in North America and Europe [5], both continue to rise in low-incidence regions such as Eastern Europe, Africa, and Eastern and Southern Asia [2, 6]. This changing epidemiology of IBD over time and geography suggests that environmental factors play a major role in pathogenesis. The present study by Amarapurkar et al. [7] is a laudable effort at understanding the epidemiological risk factors for IBD in developing countries, which would further translate into a comprehensive network of IBD interactome, and hence improve our understanding of the possible reasons for the emergence of this disease into this side of the globe.

The authors, in a prospective, multicenter case-control study, evaluated the risk factors for the development of IBD by comparing 1054 patients with IBD to 1546 matched healthy controls from Western India. They evaluated the area of residence (rural vs. urban), education (graduate vs. non-graduate), marital status, occupation (professional vs. non-professional), annual family income (< 10,000,000 Indian National Rupees, [INR] or > 10,000,000 INR), food habit (vegetarian vs. mixed diet), smoking, alcohol, and family history of IBD. The significant risk factors for ulcerative colitis (UC) included higher education, professional occupation, higher family income, being married, and appendectomy, whereas vegetarian diet was protective against UC. There was no effect of area of residence, smoking, and alcohol intake. For patients with Crohn's disease (CD), significant risk factors included the rural area of residence, being married, higher education, professional occupation, higher family income, and appendectomy. There was no effect of diet, smoking, and alcohol intake.

The effect of urbanization on the rising incidence of IBD has been demonstrated in population-based cohort studies from Canada, where from a period of 1960 to 2005, there was a progressive rise in the prevalence of both UC and CD with increasing urbanization [8], and Switzerland where living in urban zone was associated with increased risk of both UC and CD [9]. The effect of urbanization might be mediated through changes in lifestyle and behavior, environmental pollution, and changes in diet. However, studies from Asia have not replicated this observation, including the present study, and a study from China [10], which did not link urban residence with the increased risk of IBD. In fact, the present study linked rural residence with increased risk for CD which could be because of differences in patient population and geography. Studies from other parts of India and other Asian countries are required for any definite conclusion.

Effect of higher education, professional occupation, and higher income would be an indirect measure of better hygiene, and thus their association with increased risk of both CD and UC. Again, the relation of hygiene with IBD has been heterogeneous and inconsistent across the globe [11], with few studies from the West having found inverse association of IBD with number of siblings, larger family size, consumption of unpasteurized milk, bed sharing, pet ownership, and living on farms, whereas studies from India and the ACCESS study are exhibiting a heterogeneous association [12]. In a study of 200

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patients with CD from Vellore, on univariate analysis, a positive association was found with urban residence (at birth and current), availability of protected drinking water (childhood and current), availability of piped water in the house (childhood and current), and strict vegetarian dietary habit, and a negative association with regular fish consumption and the presence of cattle in the house compound [13]. On multivariate analysis, only regular fish consumption and the presence of cattle in the house had a protective association, whereas the use of safe drinking water was positively associated with CD. Another study from Northern India demonstrated that better toilet facilities and having a private bed protective against UC (contradicting the hygiene hypothesis), whereas owning a pet and stressful life events were associated with a greater risk for UC [14]. In the ACCESS study being breast fed > 12 months, antibiotic use, and daily tea or coffee consumption were protective against both UC and CD, having dogs and daily physical activity were protective only against CD, and the availability of a hot water tap and flush toilets in childhood were protective only against UC [15].

Diet is one of the major determinants of the gut microbiome, and several epidemiological studies have found both positive and negative associations between various dietary constituents and IBD [16]. Among them, higher consumption of soluble fiber (derived from fresh fruits and vegetables), vitamin D, zinc, and potassium had a protective effect against CD. There was an inconsistent negative association of ω-3 fatty acid consumption, and inconsistent positive association of ω-6 fatty acid and animal protein consumption with UC. In the present study, vegetarian diet was protective against UC, while there was no relationship with CD. However, the authors did not study the individual dietary constituents, and therefore further conclusions about the diet-IBD relationship cannot be drawn from this study.

There has been a discrepant association between smoking and IBD: positive with CD and negative with UC. However, there is increased risk of UC with former smoking and a prospective study showed that the risk of UC increased within 2–5 years after smoking cessation [17, 18]. Current smoking has also been associated with poor long-term outcomes (immunosuppression requirement, surgery, and postoperative recurrence) in patients with CD [17]. However, this association of smoking with the incident as well as developed IBD has not been consistently replicated in Asian countries, including a study from our center and the present study [19]. We recently reported that, except for hospitalization, smoking was not associated with adverse long-term outcomes in patients with CD, and the present study did not find any association between smoking and the risk of UC or CD. The possible reasons for this association of smoking with IBD and its divergence with respect to disease phenotype (UC vs. CD) and geography remains unclear, although possible hypotheses include the effect of smoking on intestinal permeability, gut microbiome, endothelial function, intestinal motility, and oxidative stress. It has been shown that mononuclear cells from smokers with CD are more susceptible to oxidative stress because of a reduced level of heat shock protein 70 [20].

Like smoking, the association between appendectomy and IBD has also been discrepant with a positive association for CD and negative for UC [17, 18]. Furthermore, appendectomy at an early age and appendectomy for appendicitis rather than for non-specific abdominal pain has been associated with incident IBD, as well as disease-related outcomes, with the direction of the outcome being like that of incident IBD. The present study, however, reported the positive association between appendectomy and both UC and CD. This observation would, however, need confirmation from other centers across India.

The association between alcohol use and the risk of IBD has again been controversial, with the literature suggesting positive, neutral and the negative association of alcohol with IBD [21]. This discrepancy could stem from differences in the geography (Asian studies suggesting a positive effect) and study design of these studies (prospective cohort study not showing any positive association).

The authors also report association between marriage and IBD; however, it is not clear from the results, whether the patients were married before or after the onset of IBD. Although the authors have not mentioned, the possible reason could be the lower age of the controls as compared to patients.

The association of positive family history with an increased risk of IBD is obvious. The rate of positive family history in the present study is like that of other studies from India and Asian countries and is considerably lower than that of West [22].

Though this study adds to the existing evidence on the interaction between environmental risk factors and IBD, it is lacking on certain fronts. There is a conflicting association of rural residence and higher education/occupation/socioeconomic status with IBD, as latter would likely be associated with urbanization. A multivariate analysis of all the individual factors could have portrayed a better picture of these associations. The effect of diet could have been better explored with the information on individual constituents.

India and other developing countries are experiencing an epidemiologic transition with a constant decline in the burden of infectious disorders, accompanied by a progressive rise in so-called 'Western diseases', being probably a result of the changing exposome, which has been characterized partially in the present study. However, we need further understanding into the intricacies of the exposome to answer the following questions: at what stage of human life are these risk factors important, what is the quantum of their risk association, the reasons for their divergent association with disease phenotype and geography, how can they be modified, and the effect of their modification on the disease burden and outcomes.

The most popular and oversimplified theory for the rapid emergence of IBD has been postulated to be hygiene hypothesis. However, hygiene as a concept has been difficult to measure as evidenced by many studies evaluating environmental risk factors for IBD in various geographical regions and coming up with divergent conclusions for risk of various environmental factors [11]. Perhaps, a more holistic model may be required rather than the reductionist approach of studying few environmental factors under the umbrella of the hygiene hypothesis. The explanatory model for the trigger of IBD should include the "whole frame shift" rather than a study of few hygiene-related factors in isolation.

The dynamic relationship between humans and their diseases has been holistically described by the epidemiological transition model [23]. This model facilitates our understanding of the evolution as well as the globalization of emerging diseases. Originally conceived by Omran [24], it visualized human and disease dynamics into three time frames, the "age of pestilence and famine," the "age of receding pandemics," and the "age of degenerative and man-made diseases." And the time frame patterns were driven by multitude factors: demographic, economic, and sociological. As per Omran's concept, we are now entering the third epidemiological transition were ecological (lifestyle) diseases and non-infectious diseases rule the roost [25]. Global emergence of IBD is probably a reflection of this holistic phenomenon for human diseases aptly termed as "The Third Epidemiological Transition."

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